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MORPHINE DEPRESSION OF VENTILATORY RESPONSE TO HYPOXIA, AND REVERSAL BY NALOXONE

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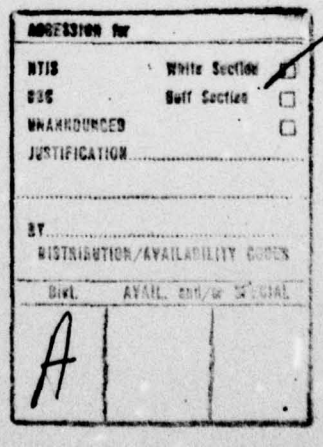
Abbreviated Title:

Morphine, Naloxone, and Hypoxic Ventilation



Key Words:

Regulation of respiration; "isocapnic" hypoxia; ventilation; narcotics: morphine; narcotic antagonists: naloxone

Abstract

Ventilatory response to 'isocapnic' hypoxia was measured in awake beagle dogs prior to and following administration of intravenous morphine sulfate, 0.6 mg/kg. Hypoxic ventilation was depressed within 30 minutes, was maximally depressed at one to two hours, and remained depressed for at least six to seven hours following the administration of morphine. Naloxone, 0.4 mg IV, completely reversed the morphine depression of the ventilatory response to hypoxia, but only transiently; 30 to 45 minutes after naloxone reversal, the ventilatory response to hypoxia was again significantly depressed. Naloxone alone demonstrated mild agonist properties on the ventilatory response to hypoxia, but the effect varied among the dogs.

Evidence accumulated during the past 25 years clearly documents that anesthetic agents,[1-4] including morphine,[5,6] depress the ventilatory response to carbon dioxide. However, it has been only in the past few years that the effect of an anesthetic agent (halothane) on the ventilatory response to hypoxia was first tested[7,8] and shown to cause significant depression. More recently, enflurane, barbiturates, and subcutaneous morphine sulfate have also been shown to depress the ventilatory response to hypoxia.[9-11]

Since anesthesiologists frequently use intravenous morphine in the immediate postoperative period, when respiratory control is of major concern, we sought to examine the effect of small doses of intravenous morphine on the ventilatory response to hypoxia, delineate the time-course of the effect, and determine the efficacy of a narcotic antagonist in reversing the effect.

Methods:

Three beagle dogs (weight range 9.3-13.1 kg) were provided with permanent tracheostomies, which were allowed to completely heal prior to the initiation of these studies. A minimum of two days elapsed prior to restudying an animal. No dog was studied more frequently than twice in one week.

The ventilatory response to rapidly progressive "isocapnic" hypoxia was measured in each dog, on each experimental day, in the awake, unmedicated condition. Complete details of the method of ventilatory testing have been published elsewhere[12,13]; however, a brief description follows. With the dog breathing through a cuffed tracheostomy tube in a closed-circle system, after establishing a resting, mildly hyperoxic (end-tidal P_{O_2}, $P_{ET}O_2$ = 200 torr) steady state, $P_{ET}O_2$ was progressively reduced to 40 torr during a five minute period, while $P_{ET}CO_2$ was held constant at 40 torr by variable bypass of a CO_2 absorber. P_{O2} and P_{CO_2} were continuously measured in the tracheostomy tube by mass spectrometry (Perkin-Elmer MGA 1100A)[14] with end-tidal values determined by an on-line digital computer (PDP 11/40) and displayed on a polygraph (Brush 200). Ventilation was measured by a Wedge Spirometer (Model 570, Med-Science Electronics, Inc.) attached to the closed-circle system by a bag-in-box, with breath-by-breath minute ventilation calculated by the on-line digital computer and displayed on the polygraph. Real-time plots of ventilation versus $P_{ET}O_2$ were displayed on a Hewlett-Packard Model 7045A X-Y recorder.

Three separate series of drug studies were conducted:

1. Time-course of effect of morphine on ventilatory response to hypoxia: two of the dogs were utilized in this series; both were tested three times each. Following determination of the unmedicated ventilatory response to rapidly progressive "isocapnic" hypoxia, morphine sulfate, 0.6 mg/kg was administered intravenously, through a previously established intravenous route. This dose of morphine produced very mild sedation in these dogs. The evaluation of the ventilatory response to hypoxia was repeated several times during the succeeding six hours.

2. Reversibility of morphine effect by naloxone: all three dogs were tested three times each in this series. After determining the unmedicated ventilatory response to rapidly progressive "isocapnic" hypoxia, morphine sulfate 0.6 mg/kg was administered intravenously through a previously established intravenous route. Forty-five minutes later, the ventilatory response to rapidly progressive "isocapnic" hypoxia was again measured. With the animal maintained at $P_{ET}O_2$ 40 torr, $P_{ET}CO_2$ 40 torr, naloxone 0.4 mg was administered intravenously, while ventilation was continuously measured. Several minutes later, the dog was returned to the normoxic condition. Thirty to forty-five minutes thereafter, the ventilatory response to rapidly progressive "isocapnic" hypoxia was again measured. The ventilatory responses among these conditions were analyzed by a factorial analysis of variance and differences between individual means were tested at the 5% level using the Least Significant Difference Criteria.[15]

3. Effect of naloxone on ventilatory response to hypoxia: all three dogs were tested three times each in this series. The ventilatory response to rapidly progressive "isocapnic" hypoxia was measured in the awake, unmedicated condition, as above. With the animal maintained at $P_{ET}O_2$ 40 torr, $P_{ET}CO_2$ 40 torr, naloxone 0.4 mg was administered intravenously, while breath-by-breath ventilation was continuously measured. Ventilation before and after the administration of naloxone was compared by use of Student's paired t-test.

Results:

Time course of effect of morphine on ventilatory response to hypoxia:

In Figure 1 is plotted the time course of the effect of morphine on the ventilatory response to hypoxia in one dog. Each point indicates the mean (±SE) of three trials. The ventilatory response was depressed within 30 minutes (earliest test) after the intravenous administration. Depression was greatest (lowest ventilatory response) one to two hours following the administration of morphine, after which the response gradually increased. Six to seven hours following administration of morphine, the ventilatory response to hypoxia had recovered to approximately 70-80% of the unmedicated values.

Reversibility of morphine effect by naloxone:

Table 1 compares for each dog, the mean (±SE) of three ventilatory responses to rapidly progressive "isocapnic" hypoxia in the unmedicated state with the three responses after morphine and the three responses after reversal with naloxone. All three dogs showed a statistically significant depression of the response 45 minutes after the intravenous administration of morphine. All three dogs exhibited a statistically significant increase in the ventilatory response three to four minutes after the administration of naloxone. The ventilatory response after reversal with naloxone was significantly greater than the unmedicated

response in two of the three dogs. Thirty to forty-five minutes after the administration of naloxone, however, the ventilatory response to hypoxia was significantly less than the response three to four minutes after naloxone administration in all three dogs, less than the unmedicated response, and greater than the response after morphine alone (statistically significant in two of the dogs).

Effect of naloxone on ventilatory response to hypoxia:

The three dogs differed in their responses to naloxone alone. Naloxone decreased the mean (±SE) ventilatory response to hypoxia of BJ (24.8 ± 1.0 to 21.3 ± 0.6 $L \cdot min^{-1}$, BTPS; $P<0.05$), increased the response of JQ (19.3 ± 2.0 to 23.0 ± 1.4 $L \cdot min^{-1}$, BTPS; $P<0.05$) and produced a statistically insignificant change in the response of PL (25.2 ± 6.0 to 22.6 ± 4.4 $L \cdot min^{-1}$, BTPS; $P>0.2$).

Discussion:

The plasma half-life of free morphine in man during the first six hours after administration is two to three hours,[16,17] with small amounts remaining detectable in the plasma for 48 hours. The analgesic effect time-course approximates the time-course of plasma concentration of morphine.[18,19] If the disposition of morphine in dogs is similar to that in man, it is not surprising that we were able to detect a depression of the ventilatory response to hypoxia during the entire six hour duration of our experiments. The ventilatory response was depressed to the greatest extent one to two hours following the intravenous administration of morphine. Weil, et al[9] also found a depressed response, greater at 60-90 minutes than at 15-30 minutes, after a subcutaneous dose of morphine; however, they did not continue their studies for longer than 90 minutes.

Naloxone, except in extremely high doses, is reported to be devoid of all narcotic agonist properties, including effects on ventilation.[20-22] However, this conclusion is based upon measurements made during unstimulated ventilation: a condition where a large variation exists around a relatively small ventilation. Jasinski, et al[21] failed to find a significant alteration by naloxone of a one point ventilatory response to carbon dioxide. We were able to elucidate an agonist effect of naloxone by investigating its effect on a respiratory system driven to a high degree of activity,

with a small variation around a relatively large ventilation. The agonist effect was variable among the three animals; stimulant in one, depressant in another, and no effect in the third. Alternatively, it is possible that naloxone alters the ventilatory response to hypoxia, but not to carbon dioxide. We did not test its effect on the latter. We have no information as to the agonist site of action: direct chemoreceptor, direct central, or indirect central, by alteration of cerebral blood flow.

Naloxone was completely effective in reversing the morphine depression of ventilatory response to hypoxia. Unfortunately, the reversal was relatively short-lived; 30-45 minutes after reversal, in two of the three dogs, more than 70% of the effect of the reversal had been lost. This length of action of naloxone is shorter than others have reported. Jasinksi, et al[23] found naloxone to be an effective prophylactic of morphine action for at least nine hours. Palminteri states that a single dose of naloxone, in dogs, is an effective reversal agent for one to two hours.[24]

Perhaps the most interesting aspect of these studies is the finding that naloxone reversal, acutely, results in a ventilatory response to "isocapnic" hypoxia, which is greater than the unmedicated control response.

Resting ventilation, after narcotic reversal, is sometimes greater than ventilation measured prior to administration of narcotic.[20] This has been attributed to an accumulation of CO_2 centrally, secondary to the rise in arterial P_{CO_2} as a result of the narcotic depressed ventilation.[20] This hypothesis does not explain our data because we maintained peripheral P_{CO_2} constant.

Several other explanations are possible [20]: (1) the narcotic antagonist has a direct respiratory stimulant activity; (2) the narcotic analgesic has both respiratory stimulant and depressant actions, and the antagonist selectively antagonizes the latter; (3) acute physical dependence is induced by the narcotic, shifting the sensitivity of the respiratory control system. Our evidence suggests that if (1) were true, the effect is mild and variable, and not sufficient to account for the consistent "rebound" effect seen in these dogs. We have no evidence regarding (2) or (3).

We offer an alternative hypothesis. If morphine decreases the cerebral vascular response to hypoxia, as has been also recently suggested by Chapman, et al,[24] central P_{CO_2} will be higher than during hypoxia without morphine, despite a similar arterial P_{CO_2} [13]. When the narcotic is reversed, there will be a central acidic stimulus greater than that which existed in the unmedicated hypoxic state. Even if cerebral blood flow were returned to the usual hypoxic value within seconds of reversal, it would be several minutes before

central P_{CO_2} approached the new steady-state value because of the two minute wash-out time of cerebral tissue.[13,26]

Although we can not directly translate these findings to man, the possibility exists that relatively small doses of morphine may markedly depress the usual increase in ventilation in response to hypoxia, and that although naloxone is capable of reversing the narcotic effect, the reversal may be of short duration.

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DISCLAIMERS

"The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense."

"In conducting the research described in this report, the investigators adherred to the 'Guide for Laboratory Animal Facilities and Care' as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences - National Research Council."

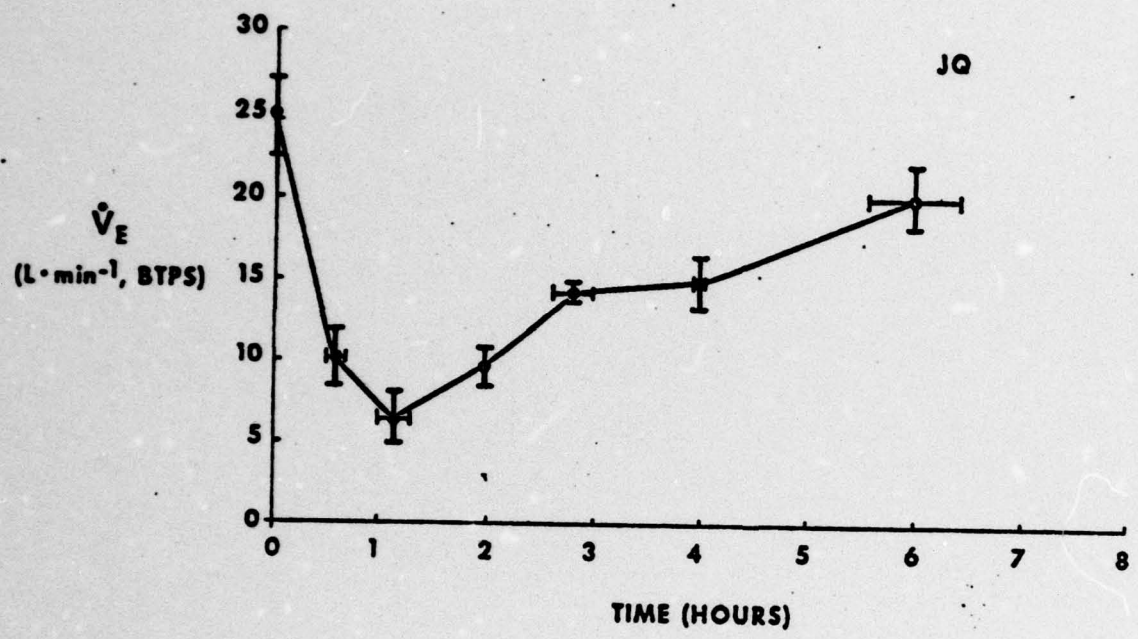
JQ
$\dot{V}_E$
(L·min^{-1}, BTPS)
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
TIME (HOURS)

Table 1

Dog #	Ventilation ($L \cdot min^{-1}$, BTPS)			
	Unmedicated	45 Min After Morphine	After Naloxone 3-4 min	After Naloxone 30-45 min
BJ	26.1 ± 1.8	19.7 ± 1.6*	34.6 ± 2.0*+	22.9 ± 2.2^{o}
JQ	19.6 ± 2.0	6.9 ± 0.7*	25.1 ± 2.5*+	12.2 ± 0.6*+o
PL	32.9 ± 0.9	12.1 ± 1.0*	32.6 ± 0.8+	26.0 ± 1.9*+o

All values are the mean ±SE of three trials.

*indicates P<0.05 versus unmedicated.
+indicates P<0.05 versus after morphine.
oindicates P<0.05 versus 3-4 min after naloxone.

LEGEND

FIGURE 1: Ventilatory response of one dog to "isocapnic" hypoxia following intravenous administration of morphine, 0.6 mg/kg. Each point represents the mean ±SE of three trials, each on a separate day.

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Regulation of respiration: "isocapnic" hypoxia; ventilation; narcotics: morphine; narcotic antagonist: naloxone

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Ventilatory response to "isocapnic" hypoxia was measured in awake dogs prior to and following administration of intravenous morphine sulfate, 0.6 mg/kg. Hypoxic ventilation was depressed within 30 minutes, was maximally depressed at one to two hours, and remained depressed for at least six to seven hours following the administration of morphine. Naloxone, 0.4 mg IV, completely reversed the morphine depression of the ventilatory response to hypoxia, but only transiently; 30 to 45 minutes after naloxone reversal, the ventilatory response to hypoxia was again

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significantly depressed. Naloxone alone demonstrated mild agonist properties on the ventilatory response to hypoxia, but the effect varied among the dogs.